Matched miRNA and mRNA signatures from an hESC-based in vitro model of pancreatic differentiation reveal novel regulatory interactions.

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Public Summary:
MicroRNAs (miRNAs) are a class of small non-coding RNAs that regulate many biological processes, including cellular differentiation. We studied the miRNA and mRNA expression profiles of hPSCs at five stages of in vitro differentiation along the pancreatic beta cell lineage. Bioinformatic analysis of the resulting data identified a unique miRNA signature in differentiated beta islet cells, and predicted the effects of key miRNAs on mRNA expression

Scientific Abstract:
The differentiation of human pluripotent stem cells (hPSCs) to insulin-expressing beta islet-like cells is a promising in vitro model system for studying the molecular signaling pathways underlying beta cell differentiation, as well as a potential source of cells for the treatment of type 1 diabetes. MicroRNAs (miRNAs) are a class of small non-coding RNAs that regulate many biological processes, including cellular differentiation. We studied the miRNA and mRNA expression profiles of hPSCs at five stages of in vitro differentiation along the pancreatic beta cell lineage (definitive endoderm, primitive gut tube, posterior foregut, pancreatic progenitor and hormone-expressing endocrine cells) in the context of samples of primary human fetal pancreas and purified adult islet cells using microarray analysis. Bioinformatic analysis of the resulting data identified a unique miRNA signature in differentiated beta islet cells, and predicted the effects of key miRNAs on mRNA expression. Many of the predicted miRNA-mRNA interactions involved mRNAs known to play key roles in the epithelial-mesenchymal transition process and pancreatic differentiation. We validated a subset of the predictions using qRT-PCR, luciferase reporter assays and western blotting, including the known interaction between miR-200 and ZEB2 (involved in epithelial-mesenchymal transition) and the novel interaction between miR-200 and SOX17 (a key transcription factor in specification of definitive endoderm). In addition, we found that miR-30d and let-7e, two miRNAs induced during differentiation, regulated the expression of RFX6, a transcription factor that directs pancreatic islet formation. These findings suggest that precise control of target mRNA expression by miRNAs ensures proper lineage specification during pancreatic development.